Atherosclerosis 245 (2016) 132–138

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Increased risk for development of coronary artery calcification in insulin-resistant subjects who developed diabetes: 4-year longitudinal study

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ARTICLE INFO

Article history:
Received 29 June 2015
Received in revised form
2 December 2015
Accepted 4 December 2015
Available online 11 December 2015

Keywords:
Coronary artery calcification
Insulin resistance
Glycemic progression

ABSTRACT

Objective: Coronary artery calcification (CAC) is considered a surrogate marker for atherosclerotic burden. The aim of this study was to analyze the risk of incident CAC associated with diabetes development in non-diabetic subjects with zero CAC score (CACS) at baseline.
Methods: 2076 non-diabetic participants (mean age 40 years) in a health screening program in whom CACS were repeatedly measured by multi-detector computed tomography in four years of intervals and with zero CACS at baseline, were retrospectively analyzed. Glycemic status was assessed in both years, with subjects divided into three groups: subjects with 'no progression', 'normal to impaired fasting glucose (IFG)' and 'progression to diabetes'. Insulin resistance was assessed by homeostasis model assessment-insulin resistance (HOMA-IR) index.
Results: Over 4 years, 204 subjects (9.8%) developed CAC. Subjects who developed diabetes showed the highest proportion of subjects with incident CAC among the three groups (21.0% vs. 9.3 and 10.4% in non-progressors and subjects from normal to IFG). The subjects with HOMA-IR level in higher half at baseline showed significantly increased risk for incident CAC in subjects who progressed from normal to IFG and in subjects who developed diabetes (1.740; 95% CI 1.014–2.985, 2.449; 95% CI 1.159–5.174) even after adjustment for confounding variables, whereas subjects with HOMA-IR level in lower half at baseline showed no significantly increased risk for incident CAC even in subjects who developed diabetes.
Conclusions: In this non-diabetic population, we found that increased risk for incident CAC in relation to diabetes development over 4 years was pronounced only in subjects with insulin resistance at baseline.

1. Introduction

Insulin resistance is known to be associated with increased cardiovascular disease risk, especially in patients with type 2 diabetes [1,2]. The presence of insulin resistance could lead to atherosclerosis via indirect and direct pathways and indicates the presence of visceral obesity and metabolic syndrome, which is a cluster of atherogenic risk factors such as dyslipidemia, hypertension, clotting disorder, and hyperglycemia [3,4]. High insulin levels could directly impair vascular function through the impairment of insulin signaling in endothelial or smooth muscle cells [3]. Some studies suggest that insulin resistance or metabolic syndrome is more closely associated with diabetes development than cardiovascular disease (CVD) [2,5].

Coronary artery calcium score (CACS) is a marker for atherosclerosis, is known to reflect the total atherosclerotic plaque burden in autopsy studies, and is considered a potential indicator of preclinical CVD [6,7]. Previous studies have demonstrated a significant correlation between CACS and the risk of future CVD development and various metabolic diseases [8–11]. In addition, large population-based cohort studies have reported a significant concordance between coronary artery calcification (CAC) prevalence/amount and CVD risk strata assessed by Framingham Risk Score (FRS) [12,13]. Recent studies are focusing on the role of 'zero

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http://dx.doi.org/10.1016/j.atherosclerosis.2015.12.010
0021-9150/

calcium' as a reliable negative predictive marker [14–16]. The use of CACS as a simple and safe surrogate marker for subclinical atherosclerosis is increasing.

Recent studies have reported an association between an increased risk of CAC and high HbA1c levels in subjects with insulin resistance [17–23]. They showed a good correlation between insulin resistance and high HbA1c with CAC development and progression. However, none of these studies longitudinally assessed the risk for CAC development in subjects without CAC and diabetes at baseline in relation with insulin resistance. Therefore, we aimed to analyze the relationship between incident CAC development and glycemic progression in non-diabetic Korean subjects with 'zero coronary calcium' over a period of 4 years. In addition, we analyzed the risk for CAC development in different groups according to baseline insulin resistance status.

2. Materials and methods

2.1. Study population

This was a retrospective longitudinal study and a part of the Kangbuk Samsung Health Study, which included participants in a medical health checkup program at the Health Promotion Center of Kangbuk Samsung Hospital, Sungkyunkwan University, Seoul, Korea. The purpose of medical health checkup programs is to promote the health of employees through regular health checkups and to enhance early detection of existing diseases. Most of the examinees are employees and family members of various industrial companies from around the country. The costs of the medical examinations are largely paid for by the employers, and a considerable proportion of examinees undergo examinations annually or biannually.

The initial study population was 2618 subjects who participated in the medical checkup program between January 2010 and December 2010 and underwent CACS measurement at baseline and repeated the medical checkup program and CACS measurement between January 2014 and December 2014. Of these subjects, 156 were excluded owing to the presence of diabetes in 2010, 8 were excluded owing to a history of ischemic stroke, 15 were excluded owing to a history of coronary artery disease, and 33 were excluded owing to missing data, resulting in a total of 2411 subjects with CACS data with two repetitive measurement of 4 years of interval. Among them, 335 subjects (13.9%) had CACS > 0 at baseline. Over four years, 22.1% of the subjects progressed to higher CACS compared as that in 4 years ago (Fig. 1). 98.5% of the subjects who had CAC at baseline progressed, whereas only 9.8% of the subjects with 'zero coronary calcium' at baseline progressed to higher CACS. After excluding 335 subjects who had CACS > 0 at baseline, final analysis included 2076 subjects.

This study was approved by the institutional review board of Kangbuk Samsung Hospital. The requirement for informed consent was waived because we used non-identified data routinely collected during the health screening process.

2.2. Anthropometric measurement and laboratory assessment

Data on medical history, medication use, and health-related behaviors were collected through a self-administered questionnaire, while physical measurements and serum biochemical parameters were obtained by trained staff during the health examinations. A current smoker was defined as a subject who replied "yes" to the question "Do you smoke currently?" in the self-questionnaire. Body weight was measured in light clothing without shoes to the nearest 0.1 kg by using a digital scale. Height was measured to the nearest 0.1 cm. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. Trained nurses measured sitting blood pressure with standard mercury sphygmomanometers.

All subjects were examined after an overnight fast. The hexokinase method was used to measure fasting serum glucose concentrations (Hitachi Modular D2400; Roche, Tokyo, Japan). An enzymatic calorimetric test was used to measure the total cholesterol and triglyceride concentrations. The selective inhibition method was used to measure the level of high-density lipoprotein cholesterol, and a homogeneous enzymatic calorimetric test was used to measure the level of low-density lipoprotein cholesterol. Serum insulin level was measured using an electrochemiluminescence immunoassay on a Modular Analytics E170 apparatus (Roche Diagnostics).

The presence of impaired fasting glucose (IFG) or diabetes mellitus was determined according to the self-questionnaire results, fasting serum blood glucose and glycated hemoglobin (HbA1c) levels of the participants, as suggested by the American Diabetes Association [24]. In brief, normoglycemia was defined by fasting seum glucose lower than 100 mg/dL, and IFG was defined as a fasting serum glucose level of 100–125 mg/dl. Diabetes was defined as a fasting serum glucose level of ≥ 126 mg/dl or HbA1c of

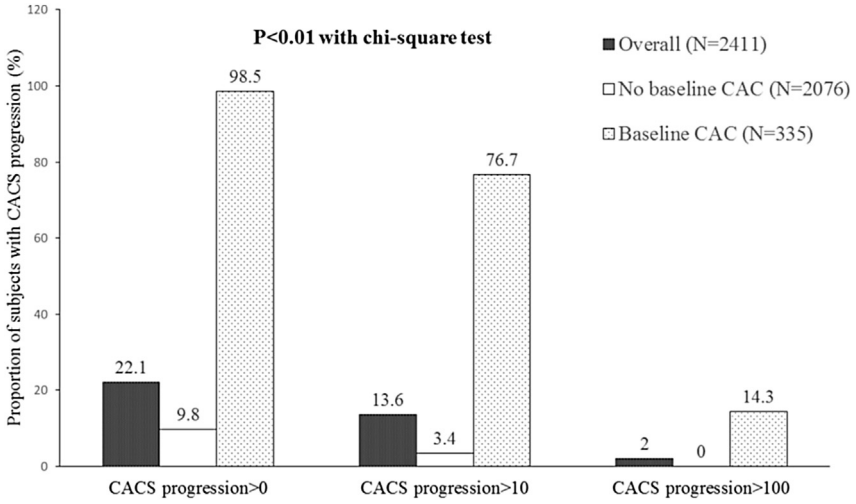

Fig. 1. Proportion of subjects with CACS progression according to baseline CACS and degree of progression over 4 years. CACS: coronary artery calcium score.